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Lipoproteins and Cardiovascular Disease: Biological Basis and Epidemiological Studies

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ABSTRACT

There is a long history to our understanding of the biological basis of lipoproteins in cardiovascular disease and to the key epidemiological studies in this field. Building on a wealth of laboratory evidence explaining the role of cholesterol and lipoproteins in the pathogenesis of atherosclerosis, epidemiological studies have characterized associations between serum lipid abnormalities and the risk of myocardial infarction. While elevation in total cholesterol has been associated with an increased risk of myocardial infarction, this information alone is not sufficient. To adequately predict cardiac risk, blood cholesterol must be further characterized by the high density lipoprotein (HDL) cholesterol present and the ratio of total cholesterol to HDL cholesterol. Several other factors, including such clinical syndromes as the "deadly quartet" of insulin resistance, central obesity, high triglycerides, and hypertension, are also associated with a markedly increased cardiac risk and should be identified; these may require unique therapeutic approaches. In addition to the costs of tertiary prevention and therapy after infarct, the impact of long-term morbidity and the economic consequences of this disease further emphasize the importance of optimizing current therapies and actual practice.

The societal impact of cardiovascular disease (CVD) is one of the most significant among medical disorders in North America today. While mortality after a myocardial infarction (MI) has been shown to vary between 7% and 15% [1], further evidence demonstrates that over half the patients surviving an infarct are left with major functional impairment resulting in work disability. Only about one third of those undergoing coronary artery revascularization by angioplasty or surgery experience an increase in left ventricular function, permitting a return to work and resumption of a normal quality of life [1]. To emphasize the importance of lipid therapy in preventing CVD and its consequences, this presentation surveys current knowledge of the biological basis of lipoproteins in CVD and highlights key epidemiological studies in this field.

Lipoprotein Mechanisms of Atherosclerosis

Coronary atherosclerosis is the etiologic condition largely responsible for ischemic heart disease. While association of long-term dyslipidemias with CVD is well established, recent evidence further suggests that acute increases in dietary fat intake impede endothelial function and reduce blood flow [2]. Elucidation of the receptor-mediated pathways for cholesterol metabolism by Brown and Goldstein demonstrated that certain abnormal low density lipoprotein (LDL) receptors mediate excessive incorporation of cholesterol into cells—a process thought to be important in the pathogenesis of atherosclerosis [3]. Building upon these findings, it was discovered that humans with abnormal variants of apoprotein E (a protein that interacts with LDL receptors) exhibit increased LDL cholesterol and triglyceride levels, predisposing these individuals to atherosclerosis and CVD [4,5]. Another recognized pathophysiologic element of atherosclerosis is cellular-level oxidation, which may mediate endothelial injury and accelerate the process of atherosclerosis. This has led to studies of the beneficial effects of antioxidants such as vitamin E.

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Epidemiologic Data

Antioxidants

Observational data from the Harvard Nurses Study showed that, while dietary intake of foods rich in antioxidant compounds (e.g., broccoli, spinach, and asparagus) had no beneficial effect, nurses who chronically ingested vitamin E supplements had a lower MI rate 8 years into the study [6]. More rigorous data from a prospective controlled trial conducted in Britain showed that vitamin E reduced the MI rate, although no change in mortality was observed [7]. Another antioxidant that has been studied in prospective clinical trials is beta-carotene, a carotinoid. These studies showed that cigarette smokers receiving beta-carotene had increased lung cancer and mortality rates [8]. Further data from the Lipid Research Clinic (LRC) Coronary Primary Prevention Trial and Follow-up Study, unlike the Harvard Nurses Study, indicated that people with high levels of natural carotinoids had a significantly lower rate of MI [9].

Across Age and Gender

Now entering its fourth generation of study population, the Framingham Heart Study first showed that young men with elevated cholesterol levels had higher MI rates [10]. With increasing age, the correlation between serum cholesterol and infarction rate was observed to be even stronger. However, the implications of elevated cholesterol for men over the age of 65 have been somewhat controversial. Following limited studies that seemed to minimize the impact of elevated cholesterol in elderly men, American College of Physician guidelines do not recommend routine measurement of serum cholesterol for those over the age of 65 [11]. But, a meta-analysis from the National Heart, Lung and Blood Institute (NHLBI) suggested that elevated cholesterol in men over age 65 was more predictive of cardiac risk than had been previously thought [12]. Given a 15-year life expectancy for those reaching age 70 without having had an MI, and a very high rate of postinfarct chronic disability, guidelines for lipid therapy above the age of 65 need to be reconsidered.

The major distinction between men and women regarding cardiac risk is the issue of pre- versus postmenopausal risk in women. While the occurrence of premenopausal coronary disease in women is quite rare and usually associated with familial hypercholesterolemia, MI rates in women generally approach those of men within 6 to 10 years after menopause [13]. In fact, in the United States, more women than men die from MIs each day.

Serum Lipoprotein and Triglyceride Measurement

While early studies correlating serum cholesterol with MI focused on total cholesterol, prediction of cardiac risk from these data is difficult to interpret for people with serum cholesterol levels between 150 and 300 mg/dL. The relative risk of MI for individuals with a total cholesterol of 300 mg/dL is about five- to six-fold greater than that of individuals with a level of 150 mg/dL. Looking at absolute risk (Fig. 1), ≈ 90% of those with total cholesterol over 300 mg/dL will suffer an MI. However, only 3% of the general population has such high total cholesterol levels. Although the absolute risk of MI for those with cholesterol levels between 150 and 200 mg/dL is only about 20%, this is where our attention should be focused, since 45% of the American population have cholesterol levels in this range and 35% of heart attacks occur in these people. The greatest number of MIs has been reported in individuals with total cholesterol levels around 225 mg/dL. However, since the absolute risk of infarction at this cholesterol level is about 40%, lipid therapy for all individuals at this level would

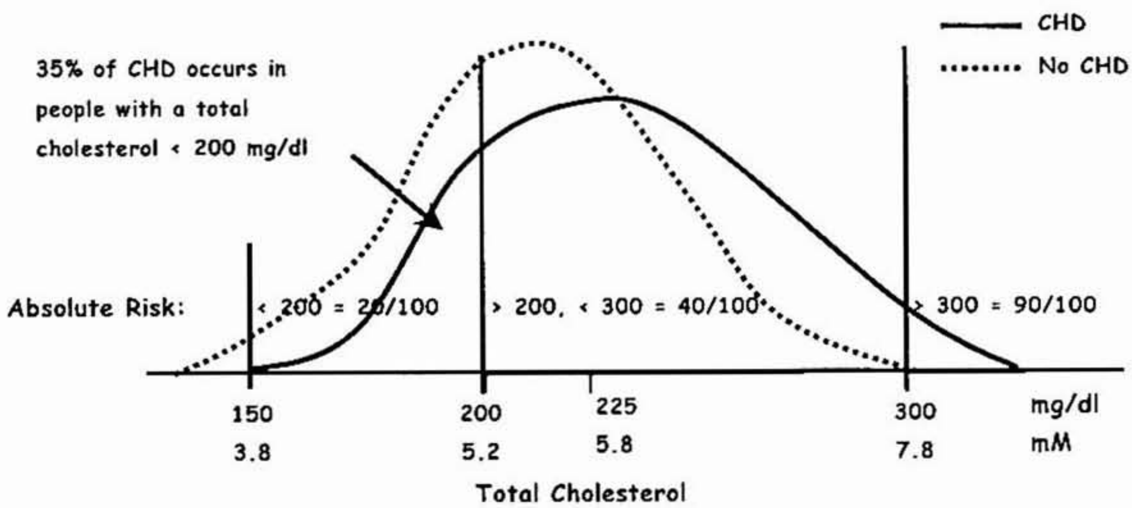

Figure 1 Coronary heart disease: relative and absolute risk. CHD, coronary heart disease.

also treat the 60% who did not require therapy. How do we target those with the greatest need?

Following more detailed analyses of the Framingham data, the National Cholesterol Education Program (NCEP) concluded that measuring high density lipoprotein (HDL) cholesterol together with total cholesterol would increase predictive value and more effectively guide decisions about lipid therapy. This recommendation is based on the observation that with increasing levels of total cholesterol, relatively low levels of HDL cholesterol are associated with greater cardiac risk, whereas higher HDL cholesterol levels appear to have a protective effect. In light of this information, a better approach to screening is to determine the ratio of total cholesterol to HDL as well as total cholesterol. Although several other types of lipoproteins have been measured and several studies have advocated the measurement of different ratios such as the LDL/HDL ratio or the LDL/total cholesterol ratio, it is likely that the most informative ratio in predicting MI is the total-cholesterol-to-HDL ratio. Our therapeutic objective for this ratio should be a value less than four. Figure 2, taken from Framingham data, illustrates the importance of this relationship between total and HDL cholesterol. The National Cholesterol Education Program 2 (NCEP2) guidelines [14] have set three LDL values as the goal of therapy: 160, 130, and 100 mg/dL. Yet, in the United States, the average LDL level of those having heart attacks is 150 mg/dL [15], while 35% of all attacks occur with a total cholesterol level less than 200 mg/dL (first row of Fig. 2) [16]. Through evaluation of total cholesterol with respect to HDL, we see a gradual increase in coronary heart disease (CHD) as total cholesterol increases, and a much more dramatic increase in CHD as HDL cholesterol decreases. This occurs at all levels of cholesterol.

In addition, current guidelines need to include other important risk factors such as hypertension, cigarette smoking, diabetes, ECG abnormalities, or left ventricular hypertrophy. The latest and best "score card" can be found from Framingham [17].

Data from the Framingham study suggest that elevated serum triglyceride levels are also associated with increased risk of infarction. While Hully et al. suggested that, after adjustment for HDL, an elevated triglyceride level was not an independent risk factor [18], data from Hockinson and Austin suggest the opposite—that after adjustment for HDL, an elevated triglyceride level was an independent risk factor [19,20]. However, as with total cholesterol, the interpretation of triglyceride levels requires knowledge of HDL cholesterol to predict cardiac risk.

Clinical Syndromes

In the search to identify individuals with lipid abnormalities and particularly high cardiac risk, specific syndromes with characteristic clinical constellations have been observed (Table 1). One such condition, characterized by insulin resistance, high triglycerides, low HDL cholesterol, and hypertension, has been described by Reaven as "Syndrome X" [21]. These metabolic disturbances are associated with several lipid abnormalities and predispose affected individuals to atherosclerosis and CVD. Despite contemporary nutritional thinking, a high-carbohydrate, low-fat diet actually exacerbates the metabolic abnormalities seen with this disorder when the total calories are ignored. Kaplan characterized this syndrome, including insulin resistance, central obesity, high triglycerides, and hypertension, as the "deadly quartet" [22].

Studies of monozygotic twins performed with the National Heart, Lung and Blood Institute showed individuals with high triglyceride and low HDL profiles had three times the risk of infarction than

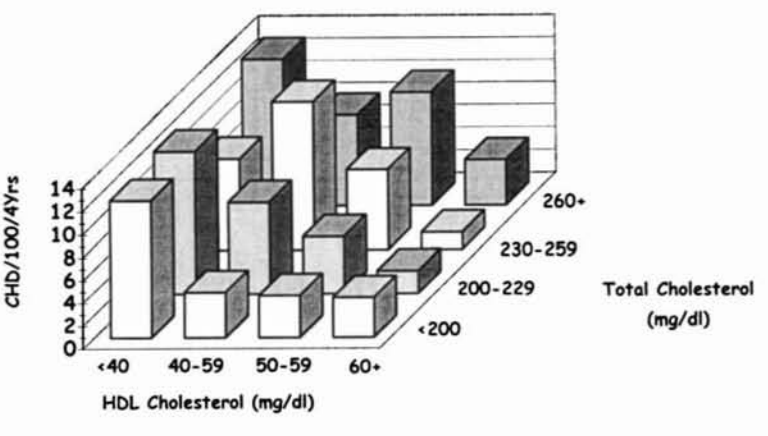

Figure 2 Coronary heart disease: total and HDL cholesterol in men and women, aged 50–79 years. CHD, coronary heart disease; HDL, high density lipoprotein. (Adapted from Framingham Heart Study/National Heart, Lung and Blood Institute data.)

Table 1 Clinical syndromes related to increased risk of coronary heart disease*

Central obesity	waist/hip ratio exceeds 0.8
Diabetes	glucose > 5.5 mM (100 mg/dL)
	insulin > 25 mU/L
	c peptide > 1.3 nM
Hypertension	BP > 140/90
Triglicerides	> 1.7 mM (150 mg/dL)
Small dense beta VLDL	yes
HDL cholesterol	< 1.17 mM (45 mg/dL)
LDL cholesterol	small dense pattern B
Uric acid	≥ 0.4 mM (7 mg/dL)
PAI-1	yes
Microalbuminuria	yes
Na/Li exchange	increased

*Syndrome X [21], Deadly Quartet [22], Dyslipidemic Hypertension [29], Insulin Resistance Syndrome (IRS) [30], and Polymetabolic Syndrome [31]. HDL, high density lipoprotein; LDL, low density lipoprotein; PAI-1, plasminogen activator-1; VLDL, very low density lipoprotein.

their normal twins. Hypertension was associated with a 4-fold risk, and individuals with the full syndrome had a 10-fold risk increase [23]. Women with the "deadly quartet" appear to be at greatest risk with twice that of other affected subgroups. Further investigation of the metabolic abnormalities of individuals has provided us with insight into the many molecular components involved in the disease process: various types of very low density lipoproteins (VLDLs), seven types of LDLs, and their dynamic relationship with HDL and triglyceride levels [24]. It has also led to the novel identification of mediators such as plasminogen activator-1 (PAI-1), little A protein (LP(a)), and elevated levels of homocysteine, all of which are implicated in accelerated thrombogenesis [25].

Conclusions

Epidemiological studies have furthered our understanding of the role of lipid abnormalities in the occurrence of CVD. Together with this epidemiological data, therapeutic trials have demonstrated the merits of lipid therapy in CVD prevention. Recent trials such as the treatment of asymptomatic men in Scotland [26] and asymptomatic men and women in Texas [27] have shown dramatic reduction in coronary heart disease, surgical procedures, and stroke, as have similar studies in secondary prevention [28]. Considering the costs of prevention and post-MI therapy, as well as the long-term morbidity and economic impact of this disease, the importance of providing and improving current lipid therapy cannot be too strongly emphasized.

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